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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,771	02/20/2002	David R. Cox	UCSF-127CIP2	4176

24353 7590 05/03/2005

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EXAMINER

CALAMITA, HEATHER

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 05/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/081,771

Applicant(s)

COX ET AL.

Examiner

Heather G. Calamita, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 March 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27-47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

RD

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Amendments of March 29, 2005 have been received and entered in full. Claims 27-47 are pending and under examination. Any objections and rejections not reiterated below are hereby withdrawn.

Terminal Disclaimer

2. The terminal disclaimer filed on March 29, 2005, disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 6,406,847 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Response to Amendment

3. The declaration under 37 CFR 1.132 filed March 29, 2005 is insufficient to overcome the rejection of claims 27-47 based upon 112 1st paragraph as set forth in the last Office action because:

Applicant speculates that molecular evolution could be used to in the methyl directed mismatch repair system of the instantly claimed invention. Dr. Cardayre simply states "there is no reason why it could not be evolved to recognize loops of significantly larger size." However Dr. Cardayer provides no evidence that the mismatch repair as disclosed in the instant application could be practiced without undue experimentation.

Claim Rejections - 35 USC § 112

4. Claims 27-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for markers with mismatches of at least 5 nucleotides where the second mismatch is four nucleotides or less, does not reasonably provide enablement for markers of four or less mismatched

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nucleotides where the second mismatch is four nucleotides or less. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention

The claims are drawn to a method of detecting mismatches by the use of in vivo mismatch repair where a second marker sequence with a mismatch is also present in a multiplex assay. The invention is in an class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The invention is a method of mismatch detection in which a mismatch between two DNA strands of interest is detected by corepair of the mismatch of interest and a mismatch of at least about 5 nucleotides in a detectable marker. The claims are broadly drawn to mismatches of any length (except for claim 39 where the mismatch is a single nucleotide polymorphism) and where the detectable marker mismatch can also be of any length.

Quantity of Experimentation

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The quantity of experimentation in this area is extremely large since there is significant variability in the activity of mismatch repair systems. Since the only mismatch repair system used requires at least 5 nucleotides in the marker sequence and less than 5 nucleotides in the corepair mismatch segment, performance of the method as current claimed, where these nucleotide requirements are absent, would require identification of a new mismatch repair system in a new organism. Screening for such a new mismatch repair system would require years of inventive effort, with many intervening steps, without any reasonable expectation that there could be effective reduction to practice in finding such a new mismatch repair system and with no guarantee of success in any of the succeeding steps.

The unpredictability of the art and the state of the prior art

The prior art of Parker et al (Proc. Natl. Acad. Sci. (1992) 89:1730-1734) teaches that mismatches of 1-4 nucleotides are repaired while mismatches of 5 nucleotides are not repaired by the E. coli dam directed mismatch system (abstract). Parker further notes that mismatches of 7, 9 and 11 bases are also not repaired by this system (page 1733, last paragraph to page 1734, first paragraph). The claimed method requires that the mutation in the detectable marker be unreparable without a second mismatch or the method will yield unpredictable results. The results will be unpredictable because the following scenarios may result. In the classic method, a 5 bp mismatch in the detectable marker and a 1 bp mismatch in the DNAs of interest will yield corepair of both and activation of the marker, while with a 5 bp mismatch in the detectable marker and no mismatch in the DNAs of interest, there will be no activation of the marker. If 3 or 4 bp mismatches are used in the detectable marker and a 1 bp mismatch occurs in the DNAs of interest, there should be corepair to yield activation of the marker. However, in the control situation here, where a 3 or 4 bp mismatch is present in the marker but no mismatch in the DNAs of interest, the E. coli dam directed mismatch system may repair the mismatch and yield activation of the marker. Thus, no information will be conveyed about the state of mismatch of the DNAs of interest because, while a null result will mean no mismatch, a positive result may or may not mean a

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mismatch is present in the DNAs of interest. The method, using 3 or 4 bp mismatches, will therefore yield an unpredictable result.

Working Examples

There are no working examples of mismatches of less than 5 nucleotides in the specification.

Guidance in the Specification.

The specification provides working examples and guidance for situations in which the mismatch in the marker gene is 5 nucleotides or greater, but provides not teaching or guidance of mismatches less than 5 nucleotides. In fact, the specification clearly states "E. coli detects single point misniatches as well as one-, two-, and three-nucleotide loops, but it does not detect loops of 5 nucleotides or more. (see page 7, lines 10-11 of the specification)."

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching against the use of less than 5 nucleotide marker mismatches by the art is opposed to patentability (see Parker). It is therefore concluded that the scope of the invention is limited to at least 5 bp mismatches in the detectable marker since a large amount of experimentation is required due to the breadth of the claim to include less than 5 bp mismatches, and since there is an absence of guidance in the specification, an absence of working examples, as well as negative teachings in the prior art of Parker and the high level of unpredictability balanced only against the high skill level in the art, it is the position of the examiner that

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it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

5. Applicants' arguments filed March 29, 2005, have been fully considered but they are not persuasive.

With respect to the 112 first paragraph rejections of claims 27-47 applicants argue one of skill in the art could readily practice the claimed invention without undue experimentation. Applicants argue the literature (Fang et al., 1997) demonstrates that *in vitro* extracts from *E. coli* are capable of initiating repair with mismatches of greater than 4 nucleotides. Applicants assert Fang et al. show there is no physical bar to the initiation of co-repair by mismatches greater than 4 nucleotides.

With respect to applicants arguments Fang et al. exemplifies an *in vitro* system the instantly claimed invention is drawn to an *in vivo* system. Additionally, Fang et al. give further support to the 112 first paragraph rejection. Fang et al. state, "Heteroduplexes with a four-base deletion are marginally repaired, and DNA with a five-base deletion is not detectably repaired by the MthHLS system (see p. 22714 3rd full paragraph) Fang et al. subsequently state that "insertions/deletions up to four or five bases were subject to Methyl directed repair at levels of 35-70% (see p. 22719 second full paragraph)." Finally Fang et al. state in the fourth full paragraph on p. 22719 that "as the base number of the insertion/deletion increased, generally the repair levels decreased." The problems with regard to directed evolution of multiple proteins *in vivo* are not trivial, as evidenced by Fang et al. The quantity of experimentation required would not be routine since only mismatch repair system used requires at least 5 nucleotides in the marker sequence and less than 5 nucleotides in the corepair mismatch segment, performance of the method as currently claimed, where these nucleotide requirements are absent, would require identification of a new mismatch repair system in a new organism, as Fang et al. clearly demonstrated in *E. coli*, as the

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base number of the insertion or deletion increases the repair level decreases. Screening for such a new mismatch repair system would require years of inventive effort, with many intervening steps, without any reasonable expectation that there could be effective reduction to practice in finding such a new mismatch repair system and with no guarantee of success in any of the succeeding steps.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Correspondence

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

hgc


JEFFREY FREDMAN
PRIMARY EXAMINER

4/28/05